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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant( )	
	10/056,788	ALLEN, JAMES	
	Examin r	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2003 and 29 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *5,6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 7-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *08/22/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 1-15 are pending examination.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-4 and 7-15) in paper filed on 8/27/03 is acknowledged.

Claims 5 and 6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse filed on 8/27/03.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 3, 4, and 7-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating hemophilia in a mammal using an rAAV virion, wherein said rAAV virion comprises an AAV-6 capsid and a heterologous nucleic acid encoding a factor IX protein operably linked to expression control elements is directly administered to at least one muscle cell in the mammal, does not reasonably provide enablement for a method of gene therapy comprising administering at least one rAAV comprising an AAV-6 capsid and a heterologous nucleic acid operably linked to expression control elements to at least

one muscle cell using any route of administration, whereby expression of said nucleic acid provides for a therapeutic effect. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The invention is directed to using a rAAV virion comprising an AAV-6 capsid in a method of gene therapy for treating any disease and/or disorder in a mammalian subject. More specifically, the invention is directed to the rAAV virion for treating blood coagulation disorders in a mammalian subject by administering the rAAV virion to muscle cells of the mammalian subject. The invention lies in the field of gene therapy.

Furthermore, and with respect to claims directed to any gene therapy directed to any treatment of a mammal; the state of the art exemplified by Anderson et al., *Nature*, Vol. 392, pp. 25-30, 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Therefore, at the time the application was filed, gene therapy was considered unpredictable.

The specification contemplates using rAAV-6 virion comprising a heterologous nucleic acid (HNA) to treat a variety of disorders and/or diseases in a mammal by administering the rAAV-6 virion to muscle cells of said mammal (see pages 10-12). The delivery of rAAV-6 to muscle cells may be by intramuscular injection or by administration into the bloodstream. The

specification teaches production of a recombinant AAV factor IX virion (Example 1, pages 16-19). The specification teaches administration of said virion to RAG-1 female immunodeficient mice (pages 19-20). The specification teaches treating hemophilia B dogs having hemophilia B using said virion (Example 3, pages 20-21). The specification contemplates hemophilia B treatment in humans with AAV6-human factor IX (page 21).

The specification provides sufficient guidance and/or factual evidence for treating hemophilia B in a mammal using rAAV-6 virion comprising a HNA encoding a factor IX protein operably linked to expression control elements. However, in view of the In Re Wands Factors, the as-filed specification does not provide sufficient guidance and/or factual evidence for one skilled in the art to use the full scope of the claimed invention. The breadth of the claimed methods embraces treating a variety of diseases and/or disorders (see pages 10-12) in a mammalian subject using rAAV-6 virion that are not taught by the prior art or the as-filed specification.

The art of record teaches several problems with gene therapy (See Rubanyi, Molecular Aspects of Medicine, Vol. 22, 2001, pages 113-142, Orkin et al., "Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy" December 7, 1995, Anderson, *supra* and Verma, *supra*).

The claimed methods recite using any route of delivery for providing said rAAV virion to muscle cells in vivo to produce a therapeutic effect. The specification teaches using intramuscular (i.m.) administration for targeting muscle cells. However, the art of record and the specification do not teach how to use any other route of administration to target said muscle cells and provide a therapeutic effect. Monahan teaches rAAV are able to transduce a wide range of

tissue types leading to gene expression several types (Molecular Medicine Today, Vol. 6, pages 433-440, 2000). Since rAAV can transduce several different types of cells in a mammal, the specification does not teach one skilled in the art how to sufficiently target enough rAAV to the muscle using any route of administration other than i.m. to produce gene expression at a therapeutic level in the muscle. In addition, treating each disease and/or disorder contemplated by the specification with the claimed method would require a certain amount of gene expression in a particular organ or tissue of the mammal. For example, some lysosomal disorders result from lack of expression of an enzyme in several tissues including the brain (e.g., Fabry disease). The specification does not teach how to express the HNA at a therapeutic effect in the brain of a mammal with the lysosomal disorder by expressing the HNA in the muscle of the mammal. The specification does not provide sufficient guidance for how to reasonably extrapolate from treating hemophilia B using i.m. injection of AAV6 virion to a method of treating any disease or disorder using any other route of administration to provide a therapeutic effect in the muscle cells for a disease and/or disorder.

In addition, with respect to using AAV6 to treat any disease or disorder contemplated by the specification, it is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement, e.g. Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997).

Furthermore, the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.

In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation in view of the art of record exemplifying the unpredictability of gene therapy, for those skilled in the art to experiment with level of HNA expression so as to provide a therapeutic effect as intended by the as-filed specification at the time the invention was made.

See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification for treating a disease and/or disorder using the claimed method; the specification does not provide reasonable detail for what protocols are required for different methods of gene therapy, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the specification to the full breadth of the claimed invention. Therefore, the as-filed specification is not enabled for the full scope of the claimed methods.

In addition, the art of record teaches problems with using rAAV in gene therapy (Monahan, *supra* and Hortelano et al., Art. Cells, Blood, Subs., and Immod. Biotech. Vol. 28, pages 1-24, 2000, and Wang et al., PNAS, Vol. 97, pages 13714-13719, 2000). The genome of AAV is only 4.7kb-5.0kb, which is too short to use for delivering some nucleic acid sequences,

e.g., full-size of hFVIII cDNA, CFTR, and the dystrophin gene. Hortelano teaches, "Despite the promising results obtained with AAV vectors delivering FIX, it has not yet been used to deliver FVIII (page 10)." Wang teaches, "AAV are too small (5kb) to package the 14-kb dystrophin cDNA (page 13714)." The specification does not teach one skilled in the art how to overcome the size limitation of AAV vectors. The specification does not provide sufficient guidance and/or factual evidence to the art used to overcome the problems with AAV size limitation.

Furthermore, claim 16 recites increasing blood-clotting efficiency in said mammalian subject using a HNA. The specification and art of record do not provide sufficient guidance to use any HNA other than blood coagulation factors (e.g., Factor IX) to increase blood-clotting efficiency in said mammalian subject.

In view of the In Re Wands Factors, it would take one skilled in the art an undue amount of experimentation to practice the full breadth of the claimed invention. As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed rAAV virion generates a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any gene therapy method as contemplated by the claims, particularly given the unpredictability of gene therapy as a whole and/or the doubts expressed in the art of record.

In conclusion, the as-filed specification and claims coupled with the art of record at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable the for a method of treating hemophilia in a mammal using an rAAV virion, wherein said rAAV virion comprises an AAV-6 capsid and a heterologous nucleic acid encoding a factor IX protein operably linked to expression control elements is directly administered to at least one

muscle cell in the mammal and not for the full breadth of the claimed methods. Given that gene therapy wherein any rAAV is employed to correct a disease or a medical condition in any mammalian subject was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any rAAV virion cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 3, 4, 7, 8, 10, 11, and 15 are rejected under 35 U.S.C. 102(e) as being anticipated by Russell et al., (US Patent 6,156,303). Russell teaches using AAV6 comprising a nucleic acid sequence to treat pathologic conditions in a mammal, including blood-clotting disorders (abstract, columns 2-3, column 17, and column 72). Russell teaches delivering AAV6 vectors to muscle cells (column 27, lines 1-15 and column 72).

Claims 1, 2, 3, 4, 7, 8, 9, 10, 11, and 15 are rejected under 35 U.S.C. 102(e) as anticipated by High et al., (IDS, US Patent 6,093,392). High teaches a method of treating hemophilia in a mammal comprising administering rAAV comprising a nucleic acid encoding Factor IX

operably linked to an expression control element to a muscle tissue of the mammal (columns 29-30). Factor IX is a human Factor IX (column 29). High teaches that any suitable AAV vector can be used in the method, including AAV1, AAV3, AAV4, and AAV6 (column 11, lines 52-57). Furthermore, High teaches targeting the skeletal muscle using the method (columns 25-26).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER